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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/445,289	MUKAMOLOVA ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *126-129,131,135-139,144 and 148-159* is/are pending in the application.

4a) Of the above claim(s) *135-139 and 151-156* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *126-129,131,144,148-150 and 157-159* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 August 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Request for Continued Examination

1) A request for continued examination under 37 C.F.R 1.114, including the fee set forth in 37 C.F.R 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R 1.114, and the fee set forth in 37 C.F.R 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R 1.114. Applicants' submission filed on 10/16/08 has been entered.

Applicants' Amendment

2) Acknowledgment is made of Applicants' amendment filed 10/16/08 in response to the final Office Action mailed 06/09/08.

Status of Claims

3) Claims 126, 144, 148 and 149 have been amended via the amendment filed 10/16/08.

New claims 157-159 have been added via the amendment filed 10/16/08.

Claims 130 and 132-134 have been canceled via the amendment filed 10/16/08.

Claims 126-129, 131, 135-139, 144 and 148-159 are pending.

Claims 151-156 have been withdrawn from consideration based upon election by original presentation. See 37 C.F.R 1.142(b) and M.P.E.P § 821.03.

Claims 126-129, 131, 144, 148-150 and 157-159 are under examination.

Prior Citation of Title 35 Sections

4) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action References.

Prior Citation of References

5) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Withdrawn

6) The objection to the specification made in paragraph 17 of the Office Action mailed 06/09/08 is withdrawn.

7) The objection to the specification made in paragraph 7(c) of the Office Action mailed 02/01/07 and maintained in paragraph 7 of the Office Action mailed 06/09/08 is withdrawn in light of Applicants' amendment to the specification.

Objection(s) Maintained

8) The objection to the specification made in paragraph 7(d) of the Office Action mailed 02/01/07 and maintained in paragraph 7 of the Office Action mailed 06/09/08 is maintained for reasons set forth therein and herein below.

Applicants contend that sequence 27 in the sequence listing filed 27 October 2006 is the same as the sequence presented in Figure 1D.

Applicants' argument has been carefully considered, but is not persuasive. The amino acid composition of SEQ ID NO: 27 in the substitute sequence listing filed 09/20/07 continues to be inconsistent with the amino acid composition of SEQ ID NO: 27 as depicted in the replaced Figure 1D filed 08/31/06. The SEQ ID NO: 27 is depicted in the replaced Figure 1D as "264 paplgeplpaapael 278 SEQ ID. N0: 27". However, the SEQ ID NO: 27 depicted on page 16 of the substitute sequence listing filed 09/20/07 depicts SEQ ID NO: 27 as "Pro Ala Pro Leu Gly Glu Pro Leu Pro Ala Ala Pro Ala **Asp** Leu" [Emphasis added]. The two sequences are inconsistent in their amino acid composition. The objection stands.

Objection to Specification

9) 37 CFR 1.75(d)(1) provides, in part, that 'the terms and phrases used in the claims must find clear support or antecedent basis in the description so that the meaning of the terms in the claims may be ascertainable by reference to the description.'

The instant specification is objected to for the following reason:

Claim 128, as amended, includes the limitations: 'bacterial cell is present in a sample' and the method identifies 'a bacterial cell in the sample'. Claim 129, as amended, includes the limitation: 'the bacterial cell is present in a patient'. New claim 159 depends from claim 128 and includes the limitation: 'the bacterial cell is from a patient'. These claims depend directly or indirectly from claim 126, which requires a step comprising 'contacting the bacterial cells with an isolated polypeptide' as recited in part (i), (ii) or (iii). This means that the bacterial cells present in a sample of a patient are to be contacted *in vivo* with an isolated polypeptide as recited in part (i),

(ii) or (iii). What is now claimed in these claims lacks clear support or antecedent basis in the specification. Note that the generic limitation 'a patient' encompasses a human or animal patient having any disease, for example, a patient having cancer, an autoimmune disease such as multiple sclerosis, heart disease, a fungal or parasitic infection, a neurologic disease, autism etc. Applicants state that support for the amendment is found at lines 24-26 of page 18; lines 1-5 of page 33; and lines 20-26 of page 34 of the specification. However, these parts of the specification do not provide antecedent basis for a method for resuscitating dormant, moribund or latent bacterial cells comprising contacting, either *in vitro* or *in vivo,* the bacterial cells in a sample of or sample from any 'patient' including a patient with a generic or specific bacterial infection, with an isolated polypeptide as recited in part (i) along with a pharmaceutically acceptable carrier, or a polypeptide as recited in part (ii) or part (iii). The identified parts of the specification do not provide antecedent basis for the instantly recited contacting step of the claimed method wherein the dormant, moribund or latent bacterial cells in a generic patient or from a generic patient are contacted *in vivo* or *in vitro* with an isolated polypeptide comprising at least 50% sequence identity with amino acid residues 117 to 184 of SEQ ID NO: 2 in a pharmaceutically acceptable carrier; or a polypeptide comprising at last 20% sequence identity with SEQ ID NO: 2; or a polypeptide comprising at least amino acid residues 117 to 184 of SEQ ID NO: 2, wherein the method resuscitates the dormant, moribund or latent bacterial cells *in vivo* in the patient, or the dormant, moribund or latent bacterial cells from the patient *in vitro*.

Rejection(s) Moot

10) The rejection of claim 130 made in paragraph 9 of the Office Action mailed 02/01/07 and maintained in paragraph 18 of the Office Action mailed 06/09/08 under 35 U.S.C § 112, first paragraph, as being non-enabled with regard to the scope, is moot in light of Applicants' cancellation of the claim.

11) The rejection of claim 130 made in paragraph 14 of the Office Action mailed 02/01/07 and maintained in paragraph 20 of the Office Action mailed 06/09/08 under 35 U.S.C. § 102(b) as being anticipated by of Mukamolova *et al.* (*Antonie van Leeuwenhoek* 67: 289-295, 1995) (Mukamolova *et al.*, 1995) as evidenced by Mukamolova *et al.* (*PNAS* 95: 8916-8921, July 1998 – Applicants' IDS) (Mukamolova *et al.*, 1998), is moot in light of Applicants' cancellation of the

claim.

Rejection(s) Withdrawn

12) The rejection of claims 148 and 149 made in paragraph 23(d) of the Office Action mailed 06/09/08 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

13) The rejection of claim 128 made in paragraph 23(c) of the Office Action mailed 06/09/08 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

14) The rejection of claims 128 and 129 made in paragraph 21 of the Office Action mailed 06/09/08 under 35 U.S.C. § 112, first paragraph, as containing new matter, is withdrawn. A new rejection is set forth below to address the claims as amended.

Rejection(s) Maintained

15) The rejection of claim 128 made in paragraph 23(a) of the Office Action mailed 06/09/08 under 35 U.S.C. § 112, second paragraph, as being indefinite, is maintained for the reasons set forth therein and herein below.

Other than stating that the claims have been amended, Applicants do not advance any substantive arguments.

Claim 128, as amended, is indefinite because it continues to have improper antecedent basis in the limitation: 'said bacterial cell' in line 1. Claim 128 depends from claim 126, which includes the pleural limitation 'bacterial cells', but not a 'bacterial cell'. For proper antecedent basis, it is suggested again that Applicants replace the above-identified limitation in line 1 of the claim with the limitation --said bacterial cells--.

16) The rejection of claim 129 made in paragraph 23(b) of the Office Action mailed 06/09/08 under 35 U.S.C. § 112, second paragraph, as being indefinite, is maintained for the reasons set forth therein and herein below.

Other than stating that the claims have been amended, Applicants do not advance any substantive arguments.

Claim 129, as amended, is indefinite because it continues to have improper antecedent basis in the limitation: 'the bacterial cell' in line 1. Claim 129 depends indirectly from claim 126, which includes the pleural limitation 'bacterial cells', but not a 'bacterial cell'. For proper antecedent basis, it is suggested again that Applicants replace the above-identified limitation in line 1 of the claim with the limitation --the bacterial cells--.

17) The rejection of claims 126-129, 131, 144 and 148-150 made in paragraph 9 of the Office Action mailed 02/01/07 and made/maintained in paragraph 18 of the Office Action mailed 06/09/08 under 35 U.S.C § 112, first paragraph, as being non-enabled with regard to the scope, is maintained for the reasons set forth therein and herein below.

New claims 157-159 are now included in this rejection.

Applicants submit the following arguments:

(a) Page 50, line 8 to page 51, line 6 of the specification describe that RP factor proteins from other bacteria, including SEQ ID NO: 2 have been identified. Lines 9-17 of page 39 describe that RP factors have been identified from specific bacteria. The alignment of RP factors as described on page 43, line 29 to page 44, line 2 and page 51, line 8 to page 52, line 5 reveals specific structural features. Methods are provided at page 45, line 16 to page 46, line 10; and page 52, lines 7-24 of the specification for assaying claimed peptides of the invention. Lines 7-24 of page 52 describe that SEQ ID NO: 2 has a biological function.

(b) The number of living cells in a bacterial culture is typically assayed by measuring (the ability of the cells to grow and divide on an agar bacterial culture plate (page 2, lines 22-23)). Certain bacterial cells may exist in a "dormant .... latent" or "moribund" state, where they cannot be cultured on agar plates under standard growth conditions (page 2, lines 24-26). Such cells are not dead, however, because they can be resuscitated (i.e., induced to grow in culture) (page 2, lines 27-28). The existence of "latent" pathogenic bacteria has important implications for human health related to bacterial infection (page 3, lines 5-7). The pathogenic bacteria, *M. tuberculosis* for example, persists for long periods of time in a "latent" state that is difficult to detect in standard diagnostic methods (page 3, lines 7-14).

(c) Using sequence information relating to *M. luteus* RP-factor, Applicant has identified RP factor proteins from other bacteria, including SEQ ID NO: 2 from M. *tuberculosis*,

that share sequence identity with *M. luteus* RP-factor (page 50, line 10, to page 51, line 6, under the header "Identification of RP-factor homologues"), and Applicant has used this information to identify conserved structural features. Specifically, Applicant has identified two RP-factors from *M. luteus* and one from *M. tuberculosis* (Figure 1A; page 34, line 21, to page 35, line 4). In addition, Applicant has identified RP-factors from *M. leprae* and *Streptomyces coelicolor*, *Streptomyces rimosus*, *Mycobacterium smegmatis*, which includes four similar genes, *Mycobacterium bovis*, and *Cornebacterium glutamicum*, which includes two similar genes (Figure 1A; page 50, line 10, to page 51, line 6). Applicant has provided an alignment of RP factor proteins in Figure 1A, which identifies conserved structural features and highly conserved amino acid residues (page 51, line 10 to page 52, line 2; Figures 9A and 9B). Applicants found that RP-factors share a secretory signal sequence and a conserved 70-residue segment that 'may' act as a signaling domain (page 51, lines 10-21, under the heading "Domain structure"). This domain includes four conserved tryptophan residues and two conserved cysteine residues that may form a disulfide bridge (page 51, line 28 to page 52, line 2). These structural features are conserved among a wide variety of proteins and are, therefore, 'likely to be functionally important'. Accordingly, Applicant's specification provides guidance relating to those regions of the protein where sequence variations are 'likely to be' tolerated and those conserved regions where variations in the sequence are less desirable. One of skill in the art could readily identify those variant polypeptides that fall within the scope of Applicants' claims. For example, Applicants' specification clearly describes methods of screening for polypeptides capable of resuscitating dormant bacteria using purified RP-factors (page 52, line 9, to page 53, line 11, page 55, line 16 to page 56, line 20). Such screening does not constitute undue experimentation because it could easily be accomplished using standard techniques that are plainly described in Applicant's specification. In analyzing what constitutes undue experimentation, the MPEP (§ 2164.06) cites *In re Wands,* (858 F.2d 731, 8 USPQ2d 1400 (Fed Cir. 1988)):

> The determination of what constitutes undue experimentation in a given case requires application of a standard of reasonableness, *having due regard for the nature of the invention and the state of the art. Ansul Co. v. Uniroyal, Inc.* (citation omitted). The test is not merely quantitative because a considerable amount of *experimentation is permissible if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.* (pg. 1404)

(d) The present situation is, in all important aspects, indistinguishable from the facts in *Wands* in which the Federal Circuit held that the applicant's claim was enabled, despite the necessity for screening, because the process of screening was straightforward. In *Wands,* the methods claimed required the use of a monoclonal antibody. During prosecution *Wands* submitted a declaration under 37 C.F.R. § 1.132 providing information about all of the hybridomas that Appellants had produced before filing the patent application. The first four fusions were unsuccessful and produced no hybridomas. The next six fusion experiments all produced hybridomas. Of all of the fusion experiments performed by *Wands*, only four of the nine fully characterized hybridomas produced antibodies that fell within the scope of the claims. *Wands* did not teach an improved method for making hybridomas. *Wands* taught and claimed a method that required the use of hybridomas having specific claimed characteristics. An additional 134 hybridoma lines were frozen and stored without further analysis. The number of these hybridomas that produce antibodies falling within the limitations of the claims is unknown.

(e) *Wands* demonstrates that routine experimentation is not always trivial or successful. Routine experimentation can include animal testing. Routine experimentation, by the nature of it being experimentation, has some aspect of uncertainty in regard to result, which is tolerable within the scope of enablement. If the experimental path and data analysis have sufficient certainty (i.e., are routine), the claims are enabled. *Wands* makes it clear that not all outcomes from routine experimentation need to fall within the scope of the claims in order for the claims to be enabled. Applicant submits that based on the level of success of *Wands*, not every peptide that falls within the scope of the claims need have the claimed activity. The Office Action notes that "Table 2 and Experiment III show that a *M. luteus* Rp-factor was able to stimulate the growth of *M. tuberculosis* cells that failed to show viability" and therefore, the specification provides enabling disclosure for the testing of peptides for the claimed activity. Using no more than routine methods, such as those provided in the specification, the skilled artisan could readily identify those polypeptides having at least 20% identity to SEQ ID NO:2 that are capable of resuscitating dormant bacteria, assigning function, or not, to protein sequences. The additional data provided by the Applicant in Exhibit A in the previous response demonstrates that testing methods for activity of peptides as RPs is routine in the art. The data also demonstrate that peptides with very low sequence identity to SEQ ID NO: 2 can have RP activity.

(f) With regard to the Office's statement with regard to claims 128-131 that the use of polypeptide variants of SEQ ID NO: 2 in therapy, prophylaxis, or diagnosis as claimed is not enabled, the claims are now directed to methods for identifying a microbial infection in a sample (claim 128) and to methods for resuscitating a bacterial cell where the cell is present in a patient 'being treated with an antimicrobial'. Applicants have clearly shown that RP-factors may be used to resuscitate bacterial cells, including dormant *M. tuberculosis* cells isolated 'from' a mouse infected with *M. tuberculosis* (page 58, line 1, to page 59, line 19). At Table 2, in Experiment III, Applicants showed that an RP-factor was able to stimulate the growth of *M. tuberculosis* cells that failed to show signs of viability (Table 2). In view of this disclosure, Applicants have clearly enabled methods of resuscitating bacterial cells in a sample or a patient.

(g) The independent claims have been amended to recite that the protein is present in a pharmaceutically acceptable carrier such that the compositions may be administrable to a subject. Dependent claims have been added reciting that the polypeptide is purified essentially to homogeneity. Therefore, the composition would be acceptable for administration to a subject. The ability to test a peptide to determine if any particular peptide would be useful for the claimed methods is not dependent on understanding the mechanism of action of the peptide. One of skill in the art can determine if there is or is not growth without understanding why there may or may not be growth of bacteria. *Wands* does not require an understanding of mechanism regarding the precise mode of functioning of an invention as long as one can test the invention and determine that it does or does not function.

Applicants' arguments have been carefully considered, but are not persuasive for the following reasons.

As set forth previously, while the instant application is enabling for an *in vitro* method of resuscitating dormant cells of homologous *Micrococcus luteus* cells in LMM, or stimulating the *in vitro* growth in Sauton medium of *Mycobacterium tuberculosis* H37Rv and stimulating the *in vitro* growth, in broth E, of *Mycobacterium smegmatis* and *Mycobacterium bovis,* comprising contacting said cells with a purified Rp factor from *Micrococcus luteus* 'Fleming strain 2665' or NCIMB 13267 strain, does not reasonably provide enablement for an *in vivo* or *in vitro* method of resuscitating dormant, moribund, or latent cells of any bacteria comprising contacting said bacterial cells with an isolated or purified polypeptide having at least 20% identity to SEQ ID NO:

2, or 50% identity with residues 117 to 184 of SEQ ID NO: 2 in a pharmaceutically acceptable carrier, or with a cell strain that comprises a nucleic acid that encodes a polypeptide having at least 20% identity to SEQ ID NO: 2, or 50% identity with residues 117 to 184 of SEQ ID NO: 2, and for a method wherein the recited polypeptide results in identification of any bacterial cell in a sample, or a sample that is from a patient or is present in a patient, as claimed broadly. The various parts of the specification pointed to by Applicants do not reasonably provide enablement for the full scope of the methods now claimed.

Applicants should note that what are claimed in the instant claims are not RP-factors from *M. luteus, M. tuberculosis, M. leprae, Streptomyces coelicolor, Streptomyces rimosus,* or *Mycobacterium smegmatis*, or their similar genes, or a biologically active SEQ ID NO: 2 from *M. tuberculosis* that shares sequence identity with *M. luteus* RP-factor; instead, a method for resuscitating dormant, moribund or latent bacterial cells of any of a plethora of pathogenic or commensal bacterial genera and bacterial species, comprising contacting the bacterial cells with an isolated polypeptide or a polypeptide purified essentially to purity wherein the polypeptide is at least 50% identical to amino acid residues 117-184 of SEQ ID NO: 2, or is at least 20% identical to SEQ ID NO: 2. The mere contacting step in the claimed method is further required to identify any generic bacterial in a sample, a sample from a patient, or a sample a patient. The resuscitation of dormant, moribund or latent homologous or heterologous bacterial cells in the claimed method is not limited to *in vitro* resuscitation, but encompasses *in vivo* resuscitation in a generically recited 'patient'. Contrary to Applicants' assertion, the claims do not require that the cell is present in a patient 'being treated with an antimicrobial'. It should be noted that except for the method of claims 157 and 158, the polypeptide used in the method of rest of the claims under examination is not required to be purified. The broad limitation 'bacterial cells' is not limited to *M. tuberculosis,* but encompasses any bacterial cells. Likewise, the limitation 'a sample' in the dependent claim 128 includes biological and non-biological samples, environmental samples, non-culture samples etc. The broad limitation 'patient' in the dependent claims 129 and 159 encompasses a human and non-human patient having any of a plethora of microbial or non-microbial infections, cancer, autoimmune diseases, neurologic diseases, autism, or medical/clinical conditions of any and all kinds. Applicants readily acknowledge that the protein is present in a pharmaceutically acceptable carrier such that the compositions may *be administrable to a subject* and that the polypeptide is

purified essentially to homogeneity such that the composition would be *acceptable for administration to a subject*. Thus, the resuscitation of bacterial cells of any pathogenic or communal bacterial genera or bacterial species from a human or animal 'patient' or present in such a 'patient' by the claimed method includes *in vivo* contacting in said patient or *in vivo* administration of the recited polypeptide variant to said patient. A polypeptide that is at least 50% identical to amino acid residues 117-184 of SEQ ID NO: 2, or at least 20% identical to SEQ ID NO: 2 is a polypeptide that is at least 50% non-identical to amino acid residues 117-184 of SEQ ID NO: 2, or at least 80% non-identical to SEQ ID NO: 2. However, there is no evidence within the instant specification that an *in vivo* or *in vitro* method of such a broad scope is enabled. Table 2 and Experiment III showing the ability of a *M. luteus* Rp-factor to stimulate the *in vitro* growth of *M. tuberculosis* cells that failed to show viability is insufficient to enable the full scope of the claimed method of identification of any bacterial cell, or the *in vivo* method encompassed within the scope of the claim. Lines 7-24 of page 52 of the specification describe that *M. luteus* Rp factor was tested for growth stimulatory activity against *M. tuberculosis*, but not SEQ ID NO: 2, a polypeptide having at least 50% sequence identity with amino acid residues 117 to 184 of SEQ ID NO: 2, a polypeptide having at least 20% sequence identity to with SEQ ID NO: 2, or a polypeptide comprising 117 to 184 of SEQ ID NO: 2. The disclosure in the specification is limited to the *in vitro* addition of a purified RP-factor protein from *M. luteus* or Rpf2 from *M. tuberculosis* to *in vitro* cultures of *M. luteus* or *M. tuberculosis,* wherein the purified protein stimulated the *in vitro* growth of cultured cells of said bacteria. See Figure 10 and also Figure 6.

It is well recognized among those of skill in the art that assigning functional activities for any particular protein or a family of proteins based upon sequence homology is inaccurate, partly because of the multifunctional nature of proteins. See abstract; and page 34 of Skolnick *et al.* (*Trends in Biotechnology* 18: 34-39, 2000, of record). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein. See abstract and Box 2 of Skolnick *et al.* In the instant application, the recited genus of polypeptide variants having at least 50% sequence identity with amino acid residues 117 to 184 of SEQ ID NO: 2 have been assigned the functional capacity of resuscitating dormant, moribund, or latent bacteria of any genus or species. However, there is no showing of a definitive nexus between murein hydrolase

activity or the alleged cell wall lytic activity of the recited genus of polypeptide variants having at least 50% sequence non-identity with amino acids 117 to 184 of SEQ ID NO: 2 and its relationship to resuscitation of dormant, moribund or latent bacterial cells, including highly virulent, pathogenic, and/or drug-resistant bacterial cells *in vivo* in a patient, or *in vitro* in a sample to identify a bacterial cell in a sample, or a sample from a generic patient, or a sample in a generic patient. Applicants only speculate that the cell wall lytic activity is 'likely' to be important for resuscitating dormant, moribund or latent bacterial cells. See paragraph bridging pages 13 and 14 of Applicants' amendment filed 08/01/07 and paragraph bridging pages 17 and 18 filed 10/16/08. Other than the purified Rp factor of *M. luteus*, there is no showing that the recited genus of isolated or purified polypeptide variants having at least 50% non-identity with amino acids 117 to 184 of SEQ ID NO: 2 or isolated or purified polypeptide variants having at least 80% non-identity with SEQ ID NO: 2 have the capacity to resuscitate dormant, moribund or latent cells of any pathogenic or commensal bacterial genera or bacterial species *in vivo* in a patient having any disease or *in vitro* in a sample, a sample from any patient, or a sample in any patient, and thereby identify said generic bacterial cells. The specific regions or amino acid residues within the amino acids spanning 117 to 184 of SEQ ID NO: 2 that are associated with the alleged capacity to resuscitate dormant, moribund or latent bacterial cells of any generic bacterial genera, *in vivo* in a patient or *in vitro* in a sample, are not identified, without which one of skill in the art would not be able to avoid alterations or substitutions in those regions, or among amino acid residues within positions 117 to 184 of SEQ ID NO: 2, while producing species of the genus of polypeptide variants having at least 50% sequence identity with amino acids 117 to 184 of SEQ ID NO: 2 or at least 20% sequence identity with SEQ ID NO: 2 in order to practice the claimed method. A domain that includes four conserved tryptophan residues and two conserved cysteine residues which 'may' form a disulfide bridge (page 51, line 28 to page 52, line 2) is not associated with the recited function of resuscitating cells of a representative species of the huge bacterial genera. Furthermore, the identification of any bacterial cell in a biological or non-biological sample or a sample in a patient or from a patient upon contacting any dormant, moribund, or latent bacterial cells of the vast genus of bacteria with the recited polypeptide variant is simply not enabled within the instant specification. The precise structure of the isolated or purified polypeptide having at least 50% identity to amino acid 117-184 of SEQ ID NO: 2 or having at least 20% sequence identity with

SEQ ID NO:2 that concurrently has the capacity to resuscitate any generic dormant, moribund, or latent bacterial cells and the precise amount of said polypeptide variant that is needed for the *in vivo* resuscitation of said dormant, moribund, or latent bacterial cells, or for the *in vitro* or *in vivo* identification of any bacterial cell in any sample is not disclosed. The alignment of the domain structures of the various proteins as depicted in Figures 9A and 9B; or the post-filing sequence identity/homology and the zymogram result submitted via Exhibit A, are insufficient to establish a clear nexus between the alleged murein hydrolase activity of the recited genus of polypeptide variants having at least 50% sequence identity with amino acids 117 to 184 of SEQ ID NO: 2, or at least 20% sequence identity with SEQ ID NO: 2, and its direct role or connection with resuscitation of dormant, moribund or latent bacterial cells, including highly virulent, pathogenic, and/or drug-resistant bacterial cells *in vivo* in a generic patient, or *in vitro* in a sample from or in a generic patient to identify a bacterial cell in a sample. Even if one produced a series of polypeptide variants falling within the scope of the instant claims and used them to contact dormant, moribund or latent, taxonomically and genetically divergent pathogenic or non-pathogenic bacterial cells *in vitro* or *in vivo*, there is no predictability that these polypeptide variants would retain the capacity to resuscitate said dormant, moribund, or latent bacterial cells *in vivo* or *in vitro,* absent a concrete showing. This is important because predictability or unpredictability is one of the *Wands* factors for enablement. The specification lacks adequate guidance and disclosure that would limit the experimentation from being undue. This is critically important because the state of the art at the time of the invention was limited to certain unsubstantiated or unproven speculations with regard to the potential use of Rpf-like proteins in detection of a bacterial cell (or diagnosis), treatment, and prophylaxis. For instance, Mukamolova *et al.* (*PNAS* 95: 8916-8921, July 1998 – Applicants' IDS) (Mukamolova *et al.*, 1998) stated that it was 'tempting to speculate' that resuscitation and growth of the very significant re-emerging pathogen *Mycobacterium tuberculosis* and possibly of *Mycobacterium leprae* 'may be' controlled in part at least by members of a family of secreted Rpf-like proteins that function as autocrine and/or paracrine growth factors. See last paragraph in left column on page 8921 of Mukamolova *et al.* (1998). In July 1998, Mukamolova *et al.* concluded as follows:

> Further experimental work will be required to explore these hypotheses, which may lead, in the short term, to substantially improved laboratory methods for the detection and cultivation of these organisms and in the longer term, to therapeutic strategies and vaccines for preventing their growth *in vivo*.

Thus, neither the instant specification, nor the state of the art at the time of the invention provides sufficient guidance and disclosure to one of skill in the art to practice the full scope of the instant invention. It is noted that Applicants have not addressed the evidence provided by the Office to establish unpredictability via the teachings of Mukamolova *et al.* (1998).

The law with regard to the unpredictability factor is clear. The predictability or unpredictability is a *Wands* factor, which cannot be dismissed in the face of what is evident from the state of the art. MPEP 2164.03 [R-2] sets forth the relationship of predictability of the art and the enablement requirement. The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The 'amount of guidance or direction' refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and if the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. See e.g., *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004). The 'predictability or lack thereof' in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability. In particular, the court in *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971), stated: [I]n the field of chemistry generally, there may be times when the well-known unpredictability of chemical reactions will alone be enough to create a reasonable doubt as to the accuracy of a particular broad statement put forward as enabling support for a claim. This will especially be the case where the statement is, on its face, contrary to generally accepted scientific principles. Most

often, additional factors, such as the teachings in pertinent references, will be available to substantiate any doubts that the asserted scope of objective enablement is in fact commensurate with the scope of protection sought and to support any demands based thereon for proof. [Footnote omitted.] In applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work. In the instant case, it is not obvious from the disclosure of the unmodified purified Rp factor of *M. luteus*, what other polypeptide variant species thereof would work *in vivo* or *in vitro*. The lack of guidance within the instant specification when taken in combination with the teachings of Mukamolova *et al*. (1998) cited above support the Office's position regarding the unpredictability factor and the need to engage in considerable amount of undue experimentation. The courts have held that it is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. See *Genentech Inc. v. Novo Nordisk A/S Ltd., 42 USPQ2d 1001)*. Moreover, the specification must have been enabling at the time the invention was made (see *In re Wright, 27 USPQ2d 1510*). A claim must be enabled over its whole breadth. In this respect, if there are doubts, substantiated by verifiable facts, there is lack of sufficient enablement. Such is the case in the instant application. In view of the art-recognized unpredictability, the lack of specific teaching and guidance in the specification, the lack of working examples enabling the full scope, the breadth of the claims, and the quantity of experimentation necessary, undue experimentation would have been required on the part of the skilled artisan to practice the full scope of the invention as claimed. The rejection stands.

18) The rejection of claims 126, 127, 131, 144, 148 and 149 made in paragraph 14 of the Office Action mailed 02/01/07 and made/maintained in paragraph 20 of the Office Action mailed

06/09/08 under 35 U.S.C. § 102(b) as being anticipated by of Mukamolova *et al.* (*Antonie van Leeuwenhoek* 67: 289-295, 1995) (Mukamolova *et al.*, 1995) as evidenced by Mukamolova *et al.* (*PNAS* 95: 8916-8921, July 1998 – Applicants' IDS) (Mukamolova *et al.*, 1998), is maintained for the reasons set forth therein and herein below.

Applicants state that filtered minimal media from the bacterial culture would include any of a number of proteins and peptides secreted by the bacteria as well as proteins from dead, lysed bacteria. Applicants submit that the numerous non-self proteins could result in a massive immune response particularly upon repeat administration. Applicants argue that any sterile solution cannot be used as a 'pharmaceutically acceptable carrier', and that even if one were to purify the protein per the methods in Mukamolova *et al*, 1998, the resulting protein would not be in a pharmaceutically acceptable carrier as now claimed. Applicants contend that minimal media cannot be considered a 'pharmaceutically acceptable carrier'. Applicants point to column 2 on page 8917 and assert that for retention of activity, the fractions were dialysed against buffer 2, which is 10 mM Tris-HCl, pH 7.4 and 10% glycerol containing 0.08M KCl. Applicants conclude that such a buffer would not be acceptable for injection. Applicants argue that as the buffer is stated to be required for activity of the protein, one would not be discouraged from altering the composition of the buffer.

Applicants' arguments have been carefully considered, but are not persuasive. The limitation 'comprising' in the phrase 'polypeptide comprising' represents open claim language. The transitional limitation 'comprising', 'including', 'containing', 'having' or 'characterized by', represents open-ended claim language and therefore, do not exclude additional, unrecited elements. See MPEP 2111.03 [R-1]. See *Moleculon Research Corp. v. CBS, Inc., 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986)*; *In re Baxter, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981)*; *Ex parte Davis, 80 USPQ 448, 450 (Bd. App. 1948)* ('comprising' leaves 'the claim open for the inclusion of unspecified ingredients even in major amounts'). Therefore, any proteins and peptides secreted by the bacteria and proteins from dead, lysed bacteria in the prior art sterile filtered supernatant comprising the isolated polypeptide of the 'Fleming strain 2665' or NCIMB 13267 strain of viable and dormant *Micrococcus luteus* are not excluded from the scope of the claims.

Applicants should note that the rejection set forth is one of anticipation and therefore one

is not required to alter the buffer composition of Mukamolova *et al.* (1995). Contrary to Applicants' assertion, repeat administration of the recited polypeptide, with or without a pharmaceutically acceptable carrier, is not a claim limitation or a step required by the claimed method.

With regard to Applicants' statement that minimal media cannot be considered a 'pharmaceutically acceptable carrier' and a Tris-HCl-containing buffer would not be acceptable for injection, the following evidence from the state of the art should be noted. First, injection or administration is not a required step of the claimed method. Second, the polypeptide recited in parts (ii) and (iii) of the independent claims 126 and 144 are not required to be present in a 'pharmaceutically acceptable carrier'. Furthermore, minimal media have been routinely used in the art as a diluent or excipient for administration of a protein to animals. For example, see part C in Example 2 of Dowling *et al.* (US 6,649,169 filed 08/13/1998). Likewise, Tris-HCl-containing carriers are routinely administered to animals as a part of a protein or a therapeutic composition. For example, see lines 61-64 in column 10 of Milstein (US 6,331,318) and the section 'Animal Model' in Example 7 of Hellner *et al.* (US 7,452,869).

As set forth previously, Mukamolova *et al.* (1995) taught a method of resuscitation of starved or dormant cells in *Micrococcus luteus* stationary cultures by contacting the dormant cells with a sterile-filtered supernatant isolated from the late log phase of viable cultures of the same *Micrococcus luteus* which supernatant contains an antibacterial factor secreted or expressed by the *Micrococcus luteus* cells, or by contacting with the resuscitating cells of *Micrococcus luteus* secreting or expressing an antibacterial factor. The antibacterial factor secreted or expressed by the *Micrococcus luteus* cells is separated from the cells and therefore is isolated. The sterile supernatant containing the non-cellular or isolated antibacterial factor is contained in a minimal medium, i.e., a pharmaceutically acceptable carrier. The sterile filtration was accomplished using a 0.22 um Millipore or Gelman filter and therefore the isolated antibacterial factor is purified to a degree. The strain of viable and dormant *Micrococcus luteus* used by Mukamolova *et al.* (1995) is the 'Fleming strain 2665' or NCIMB 13267 strain. See title; abstract; Materials and methods; paragraph bridging the two columns on page 290; Results; and Figure 2. The prior art 'Fleming strain 2665' of *Micrococcus luteus* is the very same strain used in the instant invention by Applicants (see last paragraph on page 44 of the instant application), and therefore, the prior art

strain is expected to necessarily comprise a nucleic acid that encodes the instantly recited polypeptide. Because the 'Fleming strain 2665' of *Micrococcus luteus* is the very same strain used in the instant invention by Applicants, the cells of this strain is expected to necessarily secrete or express the instantly recited polypeptide having at least 50% identity to amino acid residues 117 to 184 of SEQ ID NO: 2, and the sterile-filtered supernatant isolated from its culture is expected to necessarily contain the secreted, purified polypeptide having at least 50% identity to amino acid residues 117 to 184 of SEQ ID NO: 2. That the prior art culture supernatant necessarily comprises the instantly recited polypeptide having at least 50% identity to amino acid residues 117 to 184 of SEQ ID NO: 2 in a unit dosage form is inherent from the teachings of Mukamolova *et al.* (1995) in light of what is known in the art. For instance, Mukamolova *et al.* (1998) teach that the culture supernatant of viable cells of the 'Fleming strain 2665' of *Micrococcus luteus* contains or secretes a proteinaceous resuscitation promoting factor that comprises the instantly recited polypeptide having at least 50% identity to amino acid residues 117 to 184 of SEQ ID NO: 2 and promotes the resuscitation and growth of dormant cells of the homologous organism in picogram quantities. See abstract; Materials and Methods; Results; and Figures 2 and 3 of Mukamolova *et al.* (1998). Thus, Mukamolova *et al.* (1995) taught all of the elements of the claimed invention and therefore anticipate the instantly claimed method.

Furthermore, it should be noted that extra references and extra evidence can be used to show that the primary reference contains an enabling disclosure and that a characteristic not disclosed in the reference is inherent therein. See MPEP 2131.01. 'To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.' *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991). Note that as long as there is evidence of record establishing inherency, failure of those skilled in the art to contemporaneously recognize an inherent property, function or ingredient of a prior art reference does not preclude a finding of anticipation. *Atlas Powder Co. v. IRECO Inc.*, 190 F.3d 1342, 1349, 51 USPQ2d 1943, 1948 (Fed. Cir. 1999). Also note that the critical date of extrinsic evidence showing a universal fact need not antedate the filing date. See MPEP 2124. The rejection stands.

Rejection(s) under 35 U.S.C § 112, First Paragraph (New Matter)

19) Claims 128, 129 and 159 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 128, as amended, includes the limitations: 'bacterial cell is present in a sample, and the method identifies 'a bacterial cell in the sample'. Claim 129, as amended, includes the limitations: 'the bacterial cell is present in a patient'. New claim 159 depends from claim 128 and includes the limitation: 'the bacterial cell is from a patient'. These claims depend directly or indirectly from claim 126, which requires a step comprising 'contacting the bacterial cells with an isolated polypeptide' as recited in part (i), (ii) or (iii). This means that the bacterial cells present in a sample of a patient are to be contacted *in vivo* with an isolated polypeptide as recited in part (i), (ii) or (iii). Note that the generic limitation 'a patient' encompasses a human or animal patient having any disease, for example, a patient having cancer, an autoimmune disease such as multiple sclerosis, heart disease, a fungal or parasitic infection, a neurologic disease, autism etc. Applicants state that support for the amendment is found at lines 24-26 of page 18; lines 1-5 of page 33; lines 20-26 of page 34; and page 17, line 23 to page 18, line 10 of the specification. However, these parts of the specification do not support a method for resuscitating dormant, moribund or latent bacterial cells comprising contacting, either *in vitro* or *in vivo,* the bacterial cells in a sample of any 'patient' including a patient with generic or specific bacterial infection with an isolated polypeptide as recited in part (i) along with a pharmaceutically acceptable carrier, or in part (ii) or part (iii). These parts of the specification are not supportive of the instantly recited contacting step of the claimed method wherein the dormant, moribund or latent bacterial cells in a patient or from a patient are contacted *in vivo* or *in vitro* with an isolated polypeptide comprising at least 50% sequence identity with amino acid residues 117 to 184 of SEQ ID NO: 2 in a pharmaceutically acceptable carrier; or a polypeptide comprising at last 20% sequence identity with SEQ ID NO: 2; or a polypeptide comprising at least amino acid residues 117 to 184 of SEQ ID NO: 2, wherein the method resuscitates the dormant, moribund or latent bacterial cells *in vivo* in the patient, or from the patient *in vitro*. Therefore, the identified

limitation(s) in the claim(s) and the currently claimed scope of the claims constitute new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are invited to point to the descriptive support in specific pages and lines of the disclosure, as originally filed, for the limitation identified above, or alternatively, remove the new matter from the claim(s). Applicants should specifically point out the support for any amendments made to the disclosure. See MPEP 714.02 and 2163.06.

Rejection(s) under 35 U.S.C § 112, Second Paragraph

20) Claims 128, 129, 157 and 158 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claims 157 and 158 are vague and indefinite in the limitation: 'purified essentially to homogeneity', because it is unclear what degree of purity is encompassed in this limitation.

(b) Claim 158 is indefinite and confusing: 'wherein the polypeptide is purified essentially to homogeneity'. Claim 158 depends from claim 144, wherein dormant, moribund or latent bacterial cells are contacted with 'a cell strain expressing a nucleic acid encoding a polypeptide'. Does it mean that in claim 158 the cell strain expressing a nucleic acid is encoding a polypeptide that is purified essentially to homogeneity?

(c) Claims 128 and 129 are indefinite and confusing in the limitations: 'the method identifies a bacterial cell in the sample' and 'wherein the bacterial cell is present in a patient' respectively. Claims 128 and 129 depend directly or indirectly from claim 126, which includes contacting the bacterial cells with the isolated polypeptide recited therein. It is unclear how a mere contacting of a bacterial cell in a sample or in a patient's sample with the isolated polypeptide can identify a bacterial cell in said sample.

(d) Claims 159, which depends from claim 128, is also rejected as being indefinite because of the indefiniteness identified above in the base claim.

Rejection(s) under 35 U.S.C § 103

21) The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> **(a)** A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 148 USPQ 459, that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or unobviousness.

22) Claims 157 and 158 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Mukamolova *et al.* (*Antonie van Leeuwenhoek* 67: 289-295, 1995, of record) (Mukamolova *et al.*, 1995) as applied to claims 126 and 144 above, and further in view of Harlow *et al.* (*In*: *Antibodies*: *A Laboratory Manual*. Cold Spring Harbor Laboratory, Chapter 5, 60-71, 1988).

The teachings of Mukamolova *et al.* (1995) are explained above, which do not expressly disclose that their polypeptide is purified essentially to homogeneity.

However, methods of purifying an art-known protein or polypeptide essentially to homogeneity using an art known technique such as PAGE were routine and conventionally practiced in the art at the time of the invention. For instant, Harlow *et al.* taught how to purify a protein using PAGE technique. See page 61.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to purify the isolated polypeptide used in Mukamolova's (1995) method to homogeneity using an art-known purification technique such as PAGE taught by Harlow *et al.* to produce the instant invention. One of ordinary skill in the art would have been motivated to produce the instant invention for the expected benefit of providing Mukamolova's (1995)

polypeptide in a purified form since the use of purified reagents or products is ideally desired in the art.

Claims 157 and 158 are *prima facie* obvious over the prior art of record.

Objection(s)

23) Claims 126 and 144 are objected to for the following reasons:

(a) Claim 144 is objected to for the limitation '-' in between the limitations 'least' and 'amino acid residues' in part (iii) of the claim.

(b) Claim 144 is objected to for the limitation: 'comprising a sequence selected from …. a polypeptide'. For clarity, it is suggested that Applicants delete the limitation 'comprising a sequence' from line 3 of claim 144.

Remarks

24) Claims 126-129, 131, 144, 148-150 and 157-159 stand rejected.

It is suggested that Applicants delete the comma in line 2 of claim 126 by replacing the limitation 'comprising,' with the limitation --comprising--.

25) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. The Fax number for submission of amendments, responses and/or papers is (571) 273-8300, which receives transmissions 24 hours a day and 7 days a week.

26) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (in USA or CANADA) or 571-272-1000.

27) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached

on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's Supervisor, Robert Mondesi, can be reached on (571) 272-0956.

/S. Devi/
Primary Examiner
AU 1645

January, 2009